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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: MON 13900 - Report of the Cancer Assessment Review Committee

PC 011596

FROM: Sanjivani Diwan
Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Jessica Kidwell, Toxicologist
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Registration Division (7509C)

And

Kerry Leifer, PM Team Reviewer
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

The Cancer Assessment Review Committee met on June 16, 1999 to evaluate the carcinogenic potential of Mon 13900. Attached please find the Final Cancer Assessment Document.

cc: L. Brennecke
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CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

MON 13900

FINAL REPORT

21-SEPTEMBER-1999

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Jessica Kidwell
Jessica Kidwell, Toxicologist

DOCUMENT PREPARATION: Sanjivani Diwan
Sanjivani Diwan, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

William Burnam

Virginia Dobozy

Yiannakis Ioannou

Nancy McCarroll

Linda Taylor

Esther Rinde

Jess Rowland

Joycelyn Stewart

Clark Swentzel

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

Lucas Brennecke, Pathology Consultant

Lori Brunsman, Statistical Analysis

GUEST MEMBER IN ATTENDANCE:

Melba Morrow Branch Senior Scientist/RAB1

CONTENTS

EXECUTIVE SUMMARY

On June 16, 1999 the Cancer Assessment Review Committee (CARC) met to evaluate the carcinogenic potential of MON 13900. The studies evaluated included: 1) a 24-month combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats at dietary doses of 0, 5, 100, 1000 or 2500 (males)/2000 (females) ppm (equivalent to 0, 0.26, 5.05, 51.8, and 129.9 mg/kg/day in males and 0, 0.29, 6.03, 61.0, and 125 mg/kg/day in females, respectively) for 105 weeks; and 2) a carcinogenicity study in male and female CD-1 mice (50/sex/dose) at dietary doses of 0, 5, 40, 400, 1250, or 3500 (females only) ppm (equivalent to 0, 0.75, 5.9, 60.2 and 193 mg/kg/day in males and 0, 1.1, 8.8, 92, and 289.5 mg/kg/day in females) for 18 months.

The CARC concluded that

- The liver tumors in both sexes as well as stomach and testicular tumors in male rats were treatment-related because 1) there were significant ($p<0.01$) increasing trends for hepatocellular adenomas, carcinomas ($p<0.05$ in males) and combined adenomas/carcinomas, stomach carcinomas ($p<0.05$ in males) and combined papillomas/carcinomas ($p<0.01$ in males; $p<0.05$ in females) and testicular interstitial cell tumors in males. At 2500 ppm (129.9 mg/kg/day) male rats had increases in the incidence of adenomas and combined adenomas/carcinomas of the liver ($p<0.01$), combined papillomas/carcinomas of the stomach (non-significant) and testicular interstitial cell tumors ($p<0.05$). The CARC considered the stomach tumors as rare tumors. At 1000 ppm (51.8 mg/kg/day), male rats had an increased incidence of testicular interstitial cell tumors which was considered to be biologically significant; 2) for females, there were significant ($p<0.01$) increasing trends for hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas. Among females at 1000 and 2000 ppm (61 and 125 mg/kg/day), there were significant ($p<0.01$) increases in the incidence of hepatocellular adenomas, carcinomas (2000 ppm group only; $p<0.05$), and combined adenomas/carcinomas. No increase in the incidence of stomach tumors was noted in treated females; 3) the incidences of liver, stomach and testicular tumors in both sexes exceeded the range for the historical controls. The dosing at the highest dose was considered by the CARC to be adequate and not excessive for both sexes based on decrease in body weight gains, changes in blood cell parameters and increases in liver and kidney weights, minimal to mild liver changes and stomach hyperplasia in both sexes, as well as testicular interstitial cell hyperplasia in males.

- Liver and lung tumors in male and female mice were attributed to treatment because 1) in males, there were significant ($p<0.01$) increasing trends for hepatocellular and bronchio-alveolar adenomas and combined adenomas/carcinomas . At 1250 ppm (193 mg/kg/day) male mice had significant increases in the incidence of hepatocellular adenomas and combined

adenomas/carcinomas ($p<0.01$) as well as bronchio-alveolar adenomas ($p<0.05$). The increased incidence of bronchio-alveolar adenomas in the 400 ppm (92 mg/kg/day) males was considered to be biologically significant; 2) in females, there were significant ($p<0.01$) increasing trends for hepatocellular and bronchio-alveolar adenomas, carcinomas, and combined adenomas/carcinomas. At 3500 ppm (289.5 mg/kg/day), females had significant ($p<0.01$) increases in the incidence of hepatocellular and bronchio-alveolar adenomas, carcinomas (<0.05), and combined adenomas/carcinomas. The incidences of bronchio-alveolar adenomas, and combined adenomas/carcinomas also increased significantly at 1250 ppm (92 mg/kg/day, $p<0.01$); 3) the incidences of liver and lung tumors in both sexes exceeded the range for the historical controls. Among females, the highest dose was considered to be adequate and not excessive based on decreased body weight gain, increased liver weights and histopathological changes in the liver and lung. For males, although mortality was increased at the two higher doses, there was uncertainty as to whether the deaths could be attributed to toxicity of the chemical or to the tumors or both. Therefore, the CARC considered the dosing at the highest dose to be adequate in both sexes and not excessive.

The CARC recommended conducting an *in vitro* cytogenetic assay because MON 13900 contains a highly reactive chloroacetyl moiety and chloroacetanilide compounds, including alachlor and acetochlor, demonstrate *in vitro* clastogenicity. They cause tumors at multiple sites (liver, stomach or lung) in rats and/or mice and are classified as "likely to be carcinogenic to humans."

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified MON 13900 as **"likely to be carcinogenic to humans "** by the oral route and recommended a linear low-dose approach for human risk characterization based on the most potent of the tumor types observed in male and female rats and mice. This extrapolation is supported by the lack of data on the mode of action and inadequate data to assess the genotoxic potential.

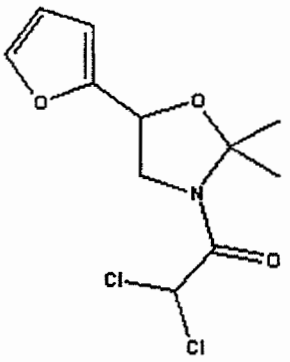
I. INTRODUCTION

On June 16, 1999, the Cancer Assessment Review Committee (CARC) met to evaluate the carcinogenic potential of MON 13900.

Ms. Jessica Kidwell of the Registration Action Branch 1 described the 24-month combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats and an 18-month carcinogenicity study in CD-1 mice by detailing the experimental design; reporting on survival and body weight effects, treatment-related non-neoplastic and neoplastic lesions, statistical analysis of the tumor data, the adequacy of dose levels tested; and presenting the weight of the evidence for the carcinogenicity of MON 13900. The registrant did not submit studies to support the mode of action for the induction of observed tumors.

II. BACKGROUND INFORMATION

MON 13900 (3-dichloroacetyl-5-(2-furanyl)-2,2-dimethyloxazolidine) is a safener used in formulations with the acetanilide herbicide acetochlor. Time-limited tolerances (expired) were established for residues of MON 13900 when used as an inert ingredient (safener) in pesticide formulations in/on corn fodder, corn forage, and corn grain at 0.01 ppm. The chemical abstract number is 121776-33-8 and the PC Code is 911596.



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III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Lemen, JK, Ruecker, FA. 1995. Combined Chronic Toxicity/Oncogenicity Study of MON 13900 Administered in Feed to Sprague-Dawley Rats for 24 Months. Monsanto Company (EHL), St. Louis, Missouri. Report No. EHL 91099; Study No. 91265. June 20, 1995. MRID No. 43700801; Document No. 013247.

A. Experimental Design

MON 13900 (95.4% a.i.) was administered in the diet to Sprague-Dawley rats (62/sex/dose) at dose levels of 0, 5, 100, 1000, or 2500 (males)/2000 (females) ppm (0, 0.26, 5.05, 51.8, and 129.9 mg/kg/day in males and 0, 0.29, 6.03, 61.0, and 125 mg/kg/day in females, respectively) for 105 weeks. An additional 10 rats/sex/dose were designated for interim sacrifice at week 52.

B. Mortality

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of MON 13900 in male or female rats.

C. Discussion of Tumor Data

The tumors of the liver, stomach and testes were evaluated and analyzed statistically. The results of the statistical analysis for each of the above tumor types (by Lori Brunsman, May 6, 1999; TXR# 013356) is presented in the following tables (Tables 1-5):

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Table 1. MON 13900 - Sprague-Dawley Rat Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	100	1000	2500
Adenomas (%)	0/61 (0)	3/60 (5)	1/60 (2)	1/58 (2)	12[a]/58 (21)
p =	0.000**	0.119	0.496	0.487	0.000**
Carcinomas (%)	3/61 (5)	0/60 (0)	2/60 (3)	3/58 (5)	5[b]/58 (9)
p=	0.036*	0.125[n]	0.508[n]	0.636	0.331
Combined (%)	3/61 (5)	3/60 (5)	3/60 (5)	4/58 (7)	16[c]/58 (28)
p =	0.000**	0.652	0.652	0.472	0.001**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before week 53. Also excludes week 52 interim sacrifice animals.

[a]First liver adenoma observed at week 88, dose 2500 ppm.
[b]First liver carcinoma observed at week 65, dose 2500 ppm.
[c]One animal in the 2500 ppm dose group had both an adenoma and a carcinoma.
[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis. There were no hepatocellular adenomas or carcinomas in any interim sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. MON 13900 - Sprague-Dawley Rat Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	100	1000	2000
Adenomas (%)	0/59 (0)	0/59 (0)	0/55 (0)	11[a]/59 (19)	17/54 (31)
p =	0.000**	1.000	1.000	0.000**	0.000**
Carcinomas (%)	0/59 (0)	0/59 (0)	0/55 (0)	2/59 (3)	4[b]/54 (7)
p=	0.002**	1.000	1.000	0.248	0.049*
Combined (%)	0/59 (0)	0/59 (0)	0/55 (0)	13/59 (22)	18[c]/54 (33)
p =	0.000**	1.000	1.000	0.000**	0.000**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice animals.

[a]First liver adenoma observed at week 69, dose 1000 ppm.
[b]First liver carcinoma observed at week 99, dose 2000 ppm.
[c]Three animals in the 2000 ppm dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. There were no hepatocellular adenomas or carcinomas in any interim sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 3. MON 13900 - Sprague-Dawley Rat Study

Male Stomach Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	100	1000	2500
Papillomas (%)	0/61 (0)	n.d.[a]	0/60 (0)	0/58 (0)	1[b]/58 (2)
p =	0.245		1.000	1.000	0.487
Carcinomas (%)	0/61 (0)	n.d.	0/60 (0)	1/58 (2)	3[c]/58 (5)
p=	0.017*		1.000	0.487	0.113
Combined (%)	0/61 (0)	n.d.	0/60 (0)	1/58 (2)	4/58 (7)
p =	0.005**		1.000	0.487	0.053

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before week 53. Also excludes week 52 interim sacrifice animals.

[a]n.d. = no data. Stomach tissues were not examined for this group.
[b]First stomach squamous cell papilloma observed at week 104, dose 2500 ppm.
[c]First stomach squamous cell carcinoma observed at week 89, dose 2500 ppm.

Note: Interim sacrifice animals are not included in this analysis. There were no stomach squamous cell papillomas or carcinomas in any interim sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. MON 13900 - Sprague-Dawley Rat Study

Female Stomach Tumor Rates[+] and Exact
Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	100	1000	2000
Papillomas (%)	0/59 (0)	0/59 (0)	0/55 (0)	0/59 (0)	1/54 (2)
p =	0.189	1.000	1.000	1.000	0.478
Carcinomas (%)	0/59 (0)	0/59 (0)	0/55 (0)	0/59 (0)	1/54 (2)
p=	0.189	1.000	1.000	1.000	0.478
Combined (%)	0/59 (0)	0/59 (0)	0/55 (0)	0/59 (0)	2/54 (4)
p =	0.035*	1.000	1.000	1.000	0.226

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before
week 53. Also excludes week 52 interim sacrifice animals.

Note: Interim sacrifice animals are not included in this analysis. There were no stomach squamous cell papillomas or carcinomas in any interim sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 5. MON 13900 - Sprague-Dawley Rat Study

Male Testicular Interstitial Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	50	100	1000	2500
Tumors (%)	2/61 (3)	3/60 (5)	0/60 (0)	5/58 (9)	10[a]/58 (17)
p =	0.000**	0.492	0.252[n]	0.199	0.012*

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before week 53. Also excludes week 52 interim sacrifice animals.

[a]First testicular tumor observed at week 83, dose 2500 ppm.

[n]Negative trend or negative change from control.

Note: Interim-sacrifice animals are not included in this analysis. There were no testicular interstitial cell tumors in any interim sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analyses

Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm group with the controls, for hepatocellular adenomas, and combined adenomas/carcinomas, all at $p < 0.01$. There was also a significant increasing trend in hepatocellular carcinomas at $p < 0.05$. A significant increasing trend in stomach carcinomas ($p < 0.05$), and combined papillomas/carcinomas ($p < 0.01$) was noted in males. Male rats also had a significant increasing trend ($p < 0.01$), and a significant difference ($p < 0.05$) in the pair-wise comparison of the 2500 ppm dose group with the controls, for testicular interstitial cell tumors. In addition at 1000 ppm, males had an increased incidence of testicular interstitial cell tumors which was considered to be biologically, although not statistically significant.

Female rats had significant increasing trends in hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 1000 and 2000 ppm groups with the controls for hepatocellular adenomas and combined adenomas/carcinomas, all at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 2000 ppm group with the controls for hepatocellular carcinomas at $p < 0.05$. There was no increase in the incidence of stomach tumors in female rats.

When compared to historical controls at the testing facility, the incidences of liver, stomach, and testicular tumors, either alone or in combination, at the high dose (as well as the incidence of male stomach and testicular tumors at the mid-dose) in the current study exceeded those of the historical controls for these tumors in the study facility. In both sexes, the incidence of liver tumors at mid-dose also exceeded the historical control range when compared with the incidences within ± 2 years (See Table 6).

Table 6. Historical Control Data for Lesions of the Liver, Stomach, and Testes in Sprague Dawley Rats

LESION	Historical Control Data within +/- 2 years (1990-1992) based on 4 studies		Complete Historical Control Data Set for lab (1982-1994) based on 19 studies	
	Total Incidence	Range	Total Incidence	Range
Liver- Males				
Adenoma	0/138 (0%)	0%	53/1057 (5%)	0-18%
Carcinoma	2/138 (1%)	0-3%	22/1057 (2%)	0-7%
Adenoma/carcinoma combined	2/138 (1%)	0-3%	70/1057 (7%)	0-22%

LESION	Historical Control Data within +/- 2 years (1990-1992) based on 4 studies		Complete Historical Control Data Set for lab (1982-1994) based on 19 studies	
	Total Incidence	Range	Total Incidence	Range
Liver - Females				
Adenoma	1/141 (1%)	0-2%	45/1061 (4%)	0-23%
Carcinoma	1/141 (1%)	0-2%	6/1061 (1%)	0-3%
Adenoma/carcinoma combined	2/141 (1%)	0-3%	51/1061 (5%)	0-25%
Stomach - Males				
Papilloma/squamous papilloma	n/a	n/a	0/982 (0%)	0%
Carcinoma, squamous cell	n/a	n/a	0/982 (0%)	0%
Papilloma/carcinoma combined	n/a	n/a	0/982 (0%)	0%
Stomach - Females				
Papilloma/squamous papilloma	n/a	n/a	1/993 (0%)	0-2%
Carcinoma, squamous cell	n/a	n/a	0/993 (0%)	0%
Papilloma/carcinoma combined	n/a	n/a	1/993 (0%)	0-2%
Testes - Males				
Interstitial Cell Tumor	3/137 (2%)	0-3%	32/998 (3%)	0-5%

n/a = not available; Data extracted from MRID No. 44842701

D. Non-Neoplastic Lesions

Numerous liver lesions (e.g., portal inflammation and pigment deposition, bile duct hyperplasia/fibrosis, sinus dilation, cystic degeneration, cystic bile ducts, eosinophilic focus, telangiectasis, and oval/stem cell hyperplasia [females only]) were observed that were significantly elevated in the high dose groups. The 1000 ppm males and females also showed significant increases in a few liver lesions, including eosinophilic focus (females only), cystic degeneration (both sexes), and telangiectasis (females only). This high incidence of liver lesions corroborates with the significant increases in liver weights, gross pathology of the organ, and elevated GGT seen in males and females at the 1000 and 2500/2000 ppm dose levels.

Both sexes exhibited kidney lesions at the 2500/2000 ppm dose levels, and females showed abnormalities at 1000 ppm. The same groups also had significant kidney enlargement and gross pathological findings. Lesions of the squamous mucosa were observed in the stomachs of 2500/2000 ppm males and females and 1000 ppm males. Testicular interstitial cell hyperplasia was significantly increased in the 2500 ppm dose males.

E. Adequacy of the Dosing for Assessment of Carcinogenicity

Survival of both sexes in all treated groups was unaffected (i.e., comparable to that of controls throughout the study). There were no treatment related clinical signs of toxicity. At the highest dose tested (2000 ppm in females/2500 ppm in males), there were decreases in body weight gains (15% below controls at 90 days, both sexes; 23% and 29% below controls at termination for males and females, respectively), depression of red blood cell parameters (RBCs, HGB, HCT), elevated GGT and cholesterol, increased liver weights (absolute/relative) (females: 36% /64% at 12-month sacrifice; 33%/64% at 24-month sacrifice: males: 25%/58% at 24-month sacrifice), increased kidney weights (absolute/relative) (males: 22%/56% at 24-month sacrifice; females: 20/57% at 24-month sacrifice), decreased adrenal weights (absolute/relative) (males: 17%/19% at 24-month sacrifice; females: 24%/26% at 24-month sacrifice), and significant increases in non-neoplastic lesions of the liver (portal inflammation and pigment deposition, bile duct hyperplasia/fibrosis, sinus dilation, cystic degeneration, cystic bile ducts, eosinophilic focus, telangiectasis, and oval/stem cell hyperplasia), as well as the kidney (brown-pigmented tubular epithelium), stomach (squamous mucosa hyperplasia and inflammation), and testes (interstitial cell hyperplasia). In addition, liver tumors occurred at a dose without severe liver changes (i.e., liver lesions at the high dose were of minimal to mild severity). The dosing at the highest dose was considered by the CARC to be adequate and not excessive based on significant decrease in body weight gains, increased absolute and/or relative liver and kidney weight, kidney nephropathy, increased GGT, decreased body weight gain, and a moderate increase in non-neoplastic liver lesions (eosinophilic focus, cystic degeneration, and telangiectasis) and stomach hyperplasia in both sexes and interstitial cell hyperplasia of testes in males.

2. Carcinogenicity Study in Mice

Reference: Lemen, JK. 1995. Oncogenicity Study of MON 13900 Administered in Feed to CD-1® Mice for 18 Months. Monsanto EHL, St. Louis, Missouri. Monsanto Study No. ML-92-038; Project No. EHL 01101, dated 6/22/95; MRID 43700802; Document No. 013247.

A. Experimental Design

CD-1 mice (50/sex/dose) were fed diets containing MON 13900 at dose levels of 0, 5, 40, 400, 1250, or 3500 (females only) ppm (0, 0.75, 5.9, 60.2 and 193 mg/kg/day in males and 0, 1.1, 8.8, 92, and 289.5 mg/kg/day in females) for 18 months. An additional 10 mice/sex/dose were designated for interim sacrifice at week 41.

B. Mortality

There was increased mortality in treated male mice, which was statistically significant at 400 and 1250 ppm. In females mice, mortality was increased (non-significantly) only at the highest dose (3500 ppm). Refer to memorandum by L. Brunsman, 1999.

C. Discussion of Tumor Data

The tumors of the liver and lung were evaluated and analyzed statistically. The following tables (Tables 7-10) present the results of the statistical analysis for each of the above tumor types (by Lori Brunsman; May 6, 1999; TXR# 013356). Statistical analyses of male and female mice were based upon Peto's Prevalence Test since there were statistically significant positive trends for mortality with increasing doses of MON 13900 in both sexes.

Table 7. MON 13900 - CD-1 Mouse Study
Male Hepatocellular Tumor Rates[+] and Peto's Prevalence
Test Results(p values)

	Dose (ppm)				
	0	5	40	400	1250
Adenomas (%)	7/46 (15)	10/49 (20)	7/50 (14)	6/49 (12)	19[a]/48 (40)
p =	0.000**	0.186	0.438	0.326	0.009**
Carcinomas (%)	1/44 (2)	1/47 (2)	1/46 (2)	0/45 (0)	2[b]/44 (5)
p =	0.241	0.471	0.478	-	0.604
Combined (%)	8/46 (17)	10[c]/49 (20)	7[c]/50 (14)	6/49 (12)	20[c]/48 (42)
p =	0.000**	0.293	-	-	0.009**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor; also excludes week 41 interim sacrifice animals.

[a]First hepatocellular adenoma not in an interim sacrifice animal observed at week 48, dose 1250 ppm.
[b]First liver carcinoma observed at week 64, dose 1250 ppm.
[c]One animal in each of the 5, 40 and 1250 ppm dose groups had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. One animal in the 1250 ppm dose group of the interim sacrifice group had a hepatocellular adenoma.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. MON 13900 - CD-1 Mouse Study
Female Hepatocellular Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)					
	0	5	40	400	1250	3500
Adenomas (%)	1/39 (3)	1/47 (2)	0/44 (0)	0/39 (0)	1[a]/45 (2)	10/41 (24)
p =	0.000**	-	-	-	-	0.009**
Carcinomas (%)	0/38 (0)	0/45 (0)	0/44 (0)	0/38 (0)	0/42 (0)	6[b]/40 (15)
p =	0.000**	-	-	-	-	0.020*
Combined (%)	1/39 (3)	1/47 (2)	0/44 (0)	0/39 (0)	1/45 (2)	12[c]/41 (29)
p=	0.000**	-	-	-	-	0.003**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before the observation of the first tumor; also excludes week 41 interim-sacrifice animals.

[a]First liver adenoma observed at week 70, dose 1250 ppm.
[b]First liver carcinoma observed at week 72, dose 3500 ppm.
[c]Four animals in the 3500 ppm group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. There were no hepatocellular adenomas or carcinomas in any interim-sacrifice animals.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. MON 13900 - CD-1 Mouse Study
Male Bronchio-Alveolar Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	5	40	400	1250
Adenomas (%)	9/45 (20)	12/47 (26)	12/48 (25)	17[a]/46 (37)	19/45 (42)
p =	0.016*	0.248	0.315	0.076	0.026*
Carcinomas (%)	4[b]/43 (9)	2/41 (5)	1/42 (2)	0/37 (0)	1/37 (3)
Combined (%)	13/45 (29)	12[c]/47 (26)	13/48 (27)	17/46 (37)	20/45 (44)
p =	0.035*	-	-	0.333	0.173

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before the observation of the first tumor; also excludes week 41 interim sacrifice animals.

[a]First bronchio-alveolar adenoma observed at week 60, dose 400 ppm.
[b]First bronchio-alveolar carcinoma observed at week 72, dose 0 ppm.
[c]Two animals in the 5 ppm dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. One animal in each of the 400 and 1250 ppm groups of the interim sacrifice group had bronchio-alveolar adenomas.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 10. MON 13900 - CD-1 Mouse Study
Female Bronchio-Alveolar Tumor Rates[+]
and Peto's Prevalence Test Results(p values)

	Dose (ppm)					
	0	5	40	400	1250	3500
Adenomas (%)	3/44 (7)	8/49 (16)	4/46 (9)	8/45 (18)	21[a]/48 (44)	14/43 (33)
p =	0.000**	0.134	0.478	0.068	0.000**	0.002**
Carcinomas (%)	0/39 (0)	2[b]/49 (4)	1/46 (2)	1/41 (2)	2/45 (4)	6/41 (15)
p =	0.006**	0.033*	0.189	0.176	0.096	0.017*
Combined (%)	3/44 (7)	10/49 (20)	5/46 (11)	9/45 (20)	22[c]/48 (46)	19[c]/43 (44)
p=	0.000**	0.027*	0.352	0.042*	0.000**	0.000**

[+]Number of tumor-bearing animals/Number of animals examined, excluding those that died before observation of the first tumor. Also excludes week 41 interim sacrifice animals.

[a]First bronchio-alveolar adenoma observed at week 60, dose 1250 ppm.
[b]First bronchio-alveolar carcinoma observed at week 68, dose 5 ppm.
[c]One animal in each of the 1250 and 3500 ppm dose groups had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. Two animals in the 1250 ppm dose group and one animal in the 3500 ppm dose group of the interim sacrifice group had bronchio-alveolar adenomas.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analyses

Male mice had significant increasing trends and significant differences in the pair-wise comparisons of the 1250 ppm dose group with the controls, for hepatocellular adenomas and combined adenomas/carcinomas, all at $p < 0.01$. Male mice also had significant increasing trends in bronchio-alveolar adenomas and combined adenomas/carcinomas, both at $p < 0.05$. There was a significant difference in the pair-wise comparison of the 1250 ppm group with the controls for bronchio-alveolar adenomas at $p < 0.05$. Additionally, the increased incidence of bronchio-alveolar adenomas in the 400 ppm males was considered to be biologically, although not statistically significant.

Female mice had significant increasing trends in hepatocellular as well as bronchio-alveolar adenomas, carcinomas, and combined adenomas/carcinomas, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 3500 ppm dose group with the controls for hepatocellular adenomas and combined adenomas/carcinomas, both at $p < 0.01$, and for hepatocellular carcinomas at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 1250 and 3500 ppm dose groups with the controls for bronchio-alveolar adenomas and combined adenomas/carcinomas, all at $p < 0.01$. In addition, there were significant differences in the pair-wise comparisons of the 5 and 3500 ppm dose groups with the controls for bronchio-alveolar carcinomas and significant differences in the pair-wise comparisons of the 5 and 400 ppm dose groups with the controls for combined bronchio-alveolar adenomas/carcinomas, all at $p < 0.05$.

When compared to historical controls at the testing facility (1987-1990 and 1990-1994[1] data), the incidences of liver and lung tumors, either alone or in combination, at the high dose in the current study exceeded those of the historical controls for these tumors at the study facility based on 10 studies in mice from each time period (See Table 11). The incidence of lung adenomas and combined adenomas/carcinomas in 1250 ppm females in the current study also exceeded that of the historical controls. In addition, the incidences of lung carcinomas and combined adenomas/carcinomas in the concurrent control males were outside the historical control range (using 1990-1994 data).

[1]Subsequent to the June 16, 1999 CARC meeting, Monsanto submitted updated historical control data (MRID No. 44857801) ranging from 1987-1996. The 1990-1994 incidence data, which are within ±2 years of the mouse study (in-life dates: 1992-1993), were extracted and presented in Table 11 along with the initial historical control data that were provided.

Table 11. Historical Control Lesions of the Liver and Lung in CD-1 Mice

LESION	TOTAL INCIDENCE[a] (%)		Range	
	1987-1990	1990-1994[b]	1987-1990	1990-1994[b]
Liver- Males				
Adenomas	43/613 (7%)	51/551 (9%)	0-16%	0-22%
Carcinomas	23/613 (4%)	12/551 (2%)	0-9%	0-5%
Adenomas/carcinomas combined	65/613(11%)	61/551 (11%)	0-20%	0-23%
Liver - Females				
Adenomas	7/607 (1%)	7/596 (1%)	0-3%	0-2%
Carcinomas	2/607 (0%)	0/596 (0%)	0-3%	0%
Adenomas/carcinomas combined	9/607 (1%)	7/596 (1%)	0-3%	0-2%
Lung - Males				
Adenomas	46/600 (8%)	62/540 (11%)	0-13%	0-25%
Carcinomas	12/600 (2%)	15/540 (3%)	0-4%	0-7%
Adenomas/carcinomas combined	57/600 (10%)	76/540 (14%)	0-15%	0-28%
Lung - Females				
Adenomas	26/599 (4%)	46/537 (9%)	0-10%	0-15%
Carcinomas	4/599 (1%)	2/537 (<1%)	0-3%	0-2%
Adenomas/carcinomas combined	30/599 (5%)	48/537 (9%)	0-10%	0-17%

[a]Total incidence is based on 10 studies from each time period.
[b]Subsequent to the June 16, 1999 CARC meeting, Monsanto submitted updated historical control data (MRID No. 44857801) ranging from 1987-1996. The 1990-1994 incidence data, which are within ±2 years of the mouse study (in-life dates: 1992-1993), were extracted and presented in Table 11 along with the initial historical control data that was provided.

D. Non-Neoplastic Lesions

The non-neoplastic lesions observed in the liver and lung of both sexes of mice are presented in Table 12.

Significant increases in several non-neoplastic lesions of the liver and lungs were noted in high dose males (1250 ppm) and females (3500 ppm). Liver lesions included hepatocellular hypertrophy of the panlobular area (males: 40% vs. 8% in controls; females: 15% (1250 ppm), 53% (3500 ppm) vs. 0% in controls), which was also significantly increased in 1250 ppm females, eosinophilic foci (males only: 28% vs. 3% in controls), bile duct hyperplasia (males: 28% vs. 0% in controls; females: 87% vs. 0% in controls), bile duct/ductule distention/ectasia (females only: 53% vs. 0% in controls), oval/stem cell hyperplasia (males: 27% vs. 0% in controls; females: 40% vs. 0% in controls), periportal hepatocellular vacuolization (females only: 70% vs. 0% in controls), and pigment deposition (females only: 82% vs. 32% in controls). Lung lesions included

chronic inflammation (males: 33% vs. 5% in controls; females: 33% (1250 ppm), 57% (3500 ppm) vs. 12% in controls), which was also significantly increased in 1250 ppm females, alveolar histiocytosis (females only: 25% vs. 5% in controls), and hyperplasia of alveolar lining cells (males only: 13% vs. 0% in controls).

Table. 12. Non-Neoplastic Lesions of the Liver and Lung in CD-1 Mice Fed MON 13900.

Lesion/Sex/Dose	0 ppm	5 ppm	40 ppm	400 ppm	1250 ppm	3500 ppm
No. Examined =	60	60	60	60	60	60
Liver- Males						
eosinophilic foci	2 (3)	1	1	0	17**(28)	–
hepatocellular hypertrophy, panlobular	5 (8)	1	2	12	24**(40)	–
hyperplasia, bile ducts	0	0	0	3	17**(28)	–
distention/ectasia, bile duct/ductule	0	0	0	0	6	–
hyperplasia, oval/stem cell	0	0	0	2	16**(27)	–
pigment deposition	10	16	14	9	13	
Liver - Females						
eosinophilic foci	0	0	0	0	0	6
hepatocellular hypertrophy, panlobular	0	2	1	2	9** (15)	32**(53)
hyperplasia, bile ducts	0	0	0	0	1	52**(87)
distention/ectasia, bile duct/ductule	0	0	0	0	1	32**(53)
hyperplasia, oval/stem cell	0	0	0	0	0	24**(40)
hepatocellular vacuolation, periportal	0	0	0	0	6	42**(70)
pigment deposition	19 (32)	22	27	24	27	49**(82)
Lung - Males						
alveolar histiocytosis	8	5	10	5	12	–
hyperplasia, alveolar lining cells	0	1	2	5	8* (13)	–
inflammation, chronic	3 (5)	5	1	10	20**(33)	–
Lung - Females						
alveolar histiocytosis	3 (5)	3	5	2	12 (20)	15**(25)
hyperplasia, alveolar lining cells	1	0	5	0	8	8
inflammation, chronic	7 (12)	4	11	9	20* (33)	34**(57)

* = $p \leq 0.05$; ** = $p \leq 0.01$

E. Adequacy of Dosing for Assessment of Carcinogenicity

An increased mortality as well as increased incidence of tumors was noted in treated male mice, which was statistically significant at 400 and 1250 ppm. In females, the mortality was actually decreased at all doses, except at 3500 ppm (non significantly) and there were increased tumor incidences at the lower doses as well. Based on the data available to the Committee, it could not be determined if the tumors in male mice were responsible for

the deaths, nor was there evidence to conclude that the deaths were due entirely to excessive toxicity, given the facts that deaths [all groups] mainly occurred during weeks 61-80 [the last interval] and the mean absolute body weights of the treated groups were similar or exceeded the mean absolute controls during the first 49 weeks. Thus, although there was increased mortality at the dose levels where increased tumor incidences occurred in males at 400 and 1250 ppm, it could not be determined whether the deaths were due to excessive toxicity, to the tumors, or to both. Therefore, the CARC agreed that tumors in male mice at these doses, could not be discounted. The CARC considered the dosing at the highest dose to be adequate in both sexes based on decreases in body weight gain (18-25%, females only), increased abdominal swelling, elevated alkaline phosphatase, alanine and aspartate aminotransferases, increased liver weights, as well as increased incidence of hepatocellular hypertrophy and chronic inflammation of the lungs.

IV. TOXICOLOGY

1. Metabolism

There are no studies available on the metabolism of MON 13900 in the rat. This is a data gap.

2. Mutagenicity

Four acceptable genotoxicity studies were available for review. Overall, the data indicate that MON 13900 induced a weak positive response at high precipitating doses in *Salmonella typhimurium* but was negative in cultured mammalian cells. MON 13900 was also negative in the mouse micronucleus assay and did not cause unscheduled DNA synthesis (UDS) in primary rat hepatocytes. The mutagenicity/genotoxicity data base, however, is not adequate and does not meet the new Subdivision F Guideline requirements for mutagenicity testing. It is recommended, therefore, that an *in vitro* cytogenetic assay be performed to satisfy current guideline requirements for mutagenicity. Furthermore, the structural similarity of MON 13900 to chloracetanilides (such as alachlor and acetochlor), which demonstrate *in vitro* clastogenicity as the major type of genotoxic activity, adds strength to this recommendation. Comments on the studies submitted are as follows:

(I) In an Ames Assay, when tested in *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 at concentrations ranging from 100-10,000 μg/plate with or without S9 fractions (Trials 1 and 2) and from 2500-10,000 μg/plate -S9 with strain TA98, reproducible and statistically significant increases in revertant colonies of strain TA100 were seen at 3000 and 10,000 μg/plate +/-S9. The effect was dose related. However, the increase in revertant colonies at 10,000 μg/plate was ≤2-fold in both trials and precipitation was noted at this level. This study is acceptable and satisfies the guideline requirements for a bacterial gene mutation assay (84-2) **(MRID No. 42019732).**

(ii) In an *in vitro* mammalian cell gene mutation assay test with Chinese hamster ovary

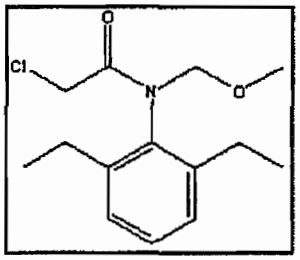
cells in both the presence and absence of metabolic activation, MON 13900 was not mutagenic under any assay condition up to a cytotoxic level (800 μg/ml -S9; 60 μg/ml +S9). This study is acceptable and satisfies the guideline requirements for an *in vitro* mammalian forward gene mutation study (84-2) **(MRID No. 42019733).**

(iii) In a mouse bone marrow micronucleus test, no increase in micronuclei was seen following intraperitoneal injections of doses up to 190 mg/kg in males and 150 mg/kg in females to CD-1 mice. Clinical toxicity, but no cytotoxicity for the target organ was seen at the highest dose tested. Thus, the study did not provide evidence that MON 13900 was clastogenic or aneugenic in this *in vivo* test system. This study is classified acceptable and satisfies the guideline requirements for *in vivo* cytogenetic mutagenicity data (84-2) **(MRID No. 42980202).**

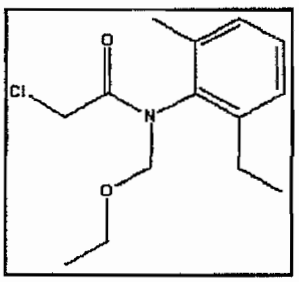
(iv) In an *in vitro* unscheduled DNA synthesis assay with rat hepatocytes, MON 13900 at concentrations ranging from 0.001 to 75 μg/ml (Trial 1) or 0.01 to 25 μg/ml (Trial 2) did not induce UDS in primary rat hepatocytes. Cytotoxicity was seen at ≥10 μg/ml in both trials. This study is acceptable and satisfies the guideline requirements for a UDS assay (84-2) **(MRID No. 42019734).**

3. Structure-Activity Relationship

MON 13900 contains a chloroacetyl moiety, which makes it highly reactive. The structurally-related chloroacetanilide compounds, alachlor and acetochlor, are both clastogenic *in vitro*. Other than sharing the reactive chloroacetyl sidechain (which could contribute to stomach cancer as the common target), there are no other structural similarities. The quinoneimine activation pathway of alachlor (and probably also of acetochlor) is not applicable to MON 13900. With the exception of stomach cancer, the target spectrum of MON 13900 differs from that of alachlor and acetolachlor. There are differences in other mechanisms (such as quinoneimine for alachlor and furan epoxide for MON 13900) of toxicity.



ALACHLOR was classified by the CARC as **"likely" to be a human carcinogen at high doses, but "not likely" at low doses, by all routes of exposure.** This conclusion was based on increased incidences of malignant and combined benign/malignant multiple tumor types (nasal epithelium, stomach and thyroid glands) in both sexes of the Long Evans rat, which occurred mainly at higher doses.



ACETOCHLOR has been classified as a **Group B2** by the HED Carcinogenicity Peer Review Committee (CPRC) based on the evidence of increased incidences of benign and malignant tumors at multiple sites in Sprague-Dawley rats (papillary adenomas of the nasal turbinates in both sexes; hepatocellular carcinomas in both sexes and thyroid follicular cell adenomas in males at excessively toxic dose levels). Also, increased incidences of benign and malignant tumors

were seen at multiple sites in Swiss albino CD-1 mice (hepatocellular carcinoma in both sexes; lung carcinomas in females; uterine histiocytic sarcoma and benign ovarian tumors in females; kidney adenomas in females).

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity -. The studies in rats and beagle dogs demonstrate liver as the target organ in both species, with hepatotoxic effects increasing in severity with increasing dose levels of MON 13900.

In a subchronic toxicity study (MRID 42019728), MON 13900 (96.4%) was administered via the diet to Sprague-Dawley rats (15/sex/dose) for 3 months at dietary levels of 5, 25, 100, 500, or 2,000 ppm (equivalent to 0.3, 2, 7, 34, or 135 mg/kg/day in males and 0.4, 2, 7, 38, or 151 mg/kg/day in females). At 500 ppm, effects included increased absolute liver weight (16%) in males, increased relative liver weights (15%, males; 12%, females), and elevated gamma glutamyltransferase (GGT) in females. At 2000 ppm, there were transient decreases in body weight gains in males, and decreased food consumption (14%, males; 10%, females), elevated serum cholesterol levels (44%, males; 37%, females), elevated GGT in both sexes, and increased absolute (37%, males; 31%, females) and relative (41%, males; 43%, females) liver weights. At 2,000 ppm, histopathologic evidence of hepatotoxicity included minimal to moderate periportal hepatocytomegaly, pericholangitis, minimal to moderate pericholangeal pigment, and minimal to slight bile duct hyperplasia in 80% to 100% of the males and females. Slight anemia in females, increased kidney- and spleen-to-body weight ratios in both sexes, and increased testes-to-body weight ratio in males were also observed at 2000 ppm, however, no compound related histopathological changes were observed in the spleen, kidney or testes. The NOAEL is 100 ppm (7 mg/kg/day). The LOAEL is 500 ppm (34/38 mg/kg/day, males/females), based on the increased absolute liver weight in males, increased liver-to-body weight ratio in males and females, and increased gamma glutamyltransferase in females. This study was classified as Acceptable/Guideline (§82-1).

In a 90-day subchronic toxicity study (MRID 42019729), MON 13900 (96.4% a.i.) was administered orally to beagle dogs (5/sex/dose) via gelatin capsules for 14 weeks at dose levels of 0, 5, 15, 50, or 150/125 mg/kg/day. The dose level of 150 mg/kg/day was lowered to 125 mg/kg/day on day 31 because of excessive toxicity. At 50 mg/kg/day, effects included increased relative liver weights (21% (50 mg/kg/day), 42% (150/125 mg/kg/day)) in females, elevated alanine aminotransferase activity in 1/5 females, and enlarged liver in 1/5 males. Changes in male and/or female liver included chronic inflammation of the bile duct in 5/5 males, bile duct hyperplasia 2/5 males and 1/5 females, and periportal fibrosis in 1/5 males. In addition to the effects noted at 50 mg/kg/day, effects seen at 150/125 mg/kg/day included elevated alanine aminotransferase in high-dose males only, increased absolute liver weight (38%) in females, and prominent hepatic reticular pattern in males (2/4, high dose vs. 1/5, controls). Histopathological

findings were similar to those seen at 50 mg/kg/day but also included hepatocellular enlargement (3/5, high dose males and females vs. 0/5, controls). Hepatotoxicity was most pronounced in the high dose dogs. The NOAEL is 5 mg/kg/day. The LOAEL for this study is 15 mg/kg/day based on bile duct inflammation in one female. This study is classified as Acceptable/Guideline (§82-1).

b) Chronic Toxicity

The summaries for the combined oral toxicity/oncogenicity study in the rat and carcinogenicity (feeding) study in the mouse are presented below. Only the "toxicological" effects are discussed; the non-neoplastic and neoplastic findings from the rat and mouse studies are not repeated here, since they were discussed earlier in this document.

In a chronic toxicity/oncogenicity study (MRID 43700801, 44842701), MON 13900 (95.4%) was administered to Sprague Dawley (CD) rats/sex/dose in the diet (see p.5 for details). At 100 ppm, increases in mean absolute (20%) and relative (21-34%) kidney weights and relative liver weight (16%) were observed in males but not females. At 1000 ppm, effects included increased absolute and relative kidney weights (males: 13% absolute, 13-38% relative; females: 16% absolute, 14% relative), increased absolute and relative liver weights (males:12% absolute, 11-34% relative; females: 26% absolute, 24% relative), increased kidney nephropathy (females only), elevated gamma glutamyl transferase (GGT), and decreased body weight gains (5-12% below controls in both sexes in the first 3 months of the study). At the highest dose tested (2000 ppm in females/2500 ppm in males), there were significant decreases in body weight gains (15-34% below controls at 90 days, both sexes; 23% and 29% (not significant) below controls at termination for males and females, respectively), depression of red blood cell parameters (RBCs, HGB, HCT), elevated GGT and cholesterol, increased absolute/relative liver (25%/58% males, 33/64% females) and kidney (22%/56% males, 22%/57% females) weights, and decreased absolute/relative adrenal weights (19/17% males, 24/26% females). The NOAEL for chronic toxicity was 5 ppm (0.26 mg/kg/day) for males and 100 ppm (6.03 mg/kg/day) for females. The LOAEL was 100 ppm (5.05 mg/kg/day) for males based on significantly increased absolute and/or relative liver and kidney weights. The LOAEL was 1000 ppm (61 mg/kg/day) for females based on significantly increased absolute and/or relative liver and kidney weight, kidney nephropathy, increased GGT, decreased body weight gain, and a moderate increase in non-neoplastic liver lesions (eosinophilic focus, cystic degeneration, and telangiectasis). The doses employed were adequate; the high doses were not excessive and the range of doses allowed observation of tumors at the LOAEL in females. This study is classified as Acceptable/Guideline (§83-5).

In another carcinogenicity study (MRID 43700802), MON 13900 (purity 97.3%) was administered to CD-1 mice/sex/dose in the diet for 18 month (refer to p. 18 for details). In 400 ppm males, there was increased mortality (number found dead at study

termination) as compared to controls (7, 11, 11, 19, 19, controls to high dose) and an increase in alanine aminotransferase (135%, 14%, 94%, 427%, low to high dose) observed at study termination. In addition at 1250 ppm, there was an increased incidence of abdominal swelling (males only), elevated alanine aminotransferase in females (-22%, -41%, -14%, 48%, 149%, low to high dose) and elevated aspartate aminotransferase (107%) in males at month 18, increased absolute and/or relative liver weights (15-35% male, 15-23% females at 9 and 18 months). At 3500 ppm, in addition to the effects mentioned above, there was increased mortality (20 vs. 16 controls), decreased cumulative body weight gains (18-25% below controls after 9 months), and elevated alkaline phosphatase (59-63%). Based on the above data, the systemic toxicity NOAEL is determined to be 40 ppm (5.9 mg/kg/day for males) and 400 ppm (92.0 mg/kg/day for females). The systemic toxicity LOAEL is 400 ppm (60.2 mg/kg/day) in males based on increased incidence of mortality and elevated alanine aminotransferase. The systemic toxicity LOAEL in females is 1250 ppm (289.5 mg/kg/day), based on increased liver weight as well as increased incidence of hepatocellular hypertrophy of the panlobular area and chronic inflammation of the lungs. This study is classified as Acceptable/Guideline (§83-2).

5. Mode of Action Studies

No studies were submitted to support the mode of action of MON 13900.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity:

- The CARC concluded that MON 13900 was carcinogenic in male and female rats because 1) there was a statistically significant increasing trend ($p<0.01$)) in the incidence of liver adenoma, carcinoma ($p<0.05$ in males) and combined adenoma/carcinoma in both sexes with increasing dose; 2) there was also increased incidence of liver adenoma and combined adenoma/carcinoma in high-dose males (adenoma: 12/58, 21% vs 0/61, 0% in controls; combined: 16/58, 28% vs 3/61, 5%) and mid- and high-dose females (adenoma: 11/59, 19% and 17/54, 31%, respectively, vs 0/59, 0% in controls; combined: 13/59, 22% and 18/54, 33%, respectively, vs 0/59, 0% in controls) as well as increased incidence of liver carcinoma in high-dose females (carcinoma: 4/54, 7% vs 0/59, 0% in controls). The increased incidences were statistically significant by pair-wise comparisons of the above dose groups with the controls; 3) the incidence of above liver tumors in males at 1000 and 2500 ppm and females at 1000 and 2000 ppm exceeded the range for historical controls (males: 0% (adenomas); 0%-3% (carcinomas), and 0%-3% (combined); females: 0%-2% (adenomas), 0%-2%(carcinomas) and 0%-3% (combined)). 4) tumors were seen without severe non-neoplastic liver changes;

There were significant increasing trends for stomach carcinomas ($p<0.01$ in males; $p<0.05$ in females) and combined papillomas/carcinomas ($p<0.01$ in males; $p<0.05$ in females). In high-dose males, the incidences of these tumors (carcinomas: 5%; combined: 7% vs 0% in controls) were outside the historical control range (0%).

A significant increase in testicular interstitial cell tumors was noted at 2500 ppm among males (10/58, 17% , $p<0.05$ vs 2/61, 3% in controls) along with a dose-related increasing trend ($p<0.01$). The incidence at 1000 ppm (5/58, 9%) was considered by the CARC to be biological significant. The incidences at 1000 (9%) and 2500 ppm (17%) exceeded the historical control range (0%-5%).

Dosing at the highest dose was considered by the CARC to be adequate and not excessive based on decreases in body weight gains (15% below controls at 90 days, both sexes; 23% and 29% below controls at termination for males and females, respectively), increased liver and kidney weights and non-neoplastic changes including eosinophilic foci and cystic degeneration of the liver, bile duct hyperplasia, hyperplasia of squamous mucosa of the stomach, interstitial cell hyperplasia and nephropathy. Based on the above weight-of-the-evidence, the **CARC concluded** that the liver tumors at 2500 ppm in males and at 1000 and 2000 ppm in females as well as rare tumors including stomach and testicular tumors in 2500 ppm group male rats were treatment-related.

- In the mouse carcinogenicity study, administration of MON 13900 in the diet was associated with a significant increase in liver and lung tumors in both sexes because: 1) a significant increasing trend was noted for hepatocellular adenoma and combined adenoma/carcinoma for both sexes and carcinomas for females, all at $p<0.01$. There was a treatment-related increase in the incidence of liver adenoma and combined adenoma/carcinoma at 1250 ppm in males (adenoma: 19/48, 40% vs 7/46, 15% in controls; combined: 20/48, 42% vs 8/46, 17%) and of liver adenoma, carcinoma, and combined adenoma/carcinoma at 3500 ppm in females (adenoma: 10/41, 24% vs 1/39, 3% in controls; carcinoma: 6/40, 15% vs 0/38, 0% in controls; combined: 12/41, 29% vs 1/39, 3% in controls). The increased incidence was statistically significant by pair-wise comparison of the above dose groups with controls; 2) there were significant increasing trends ($p<0.05$ in males; $p<0.01$ in females) in the incidence of bronchio alveolar adenoma and combined adenoma/carcinoma (in both sexes), as well as carcinoma (in females) with increasing dose. There was increased incidence in pair-wise comparison of the 1250 ppm dose group with the controls, for bronchio-alveolar adenoma in males (adenoma: 19/45, 42% vs 9/45, 20% in controls) and at 3500 ppm for adenomas, carcinomas, and combined adenoma/carcinoma in females (adenoma: 14/43, 33%, $p<0.01$ vs 3/44, 7% in controls; carcinoma: 6/41, 15%, $p<0.05$ vs 0/39, 0% in controls; combined: 19/43, 44% vs 3/44, 7% in controls).and 3) the incidences of above lung tumors at 1250 ppm in males and at

3500 ppm in females exceeded the range for historical controls (males: 0%-25%; females 0%-15%; carcinomas: females: 0%-2%; combined: females: 0%-17%).

For males, although mortality was increased at the two higher doses, there was uncertainty as to whether the deaths could be attributed to toxicity of the chemical or to the tumors or both. In females, there was a significant increasing trend for mortality, but no significant difference in pair-wise comparisons of the dosed groups with the controls. The CARC considered the dosing at the highest dose to be adequate in both sexes based on occurrence of mortality, significant decreases in body weight gain (18-25%, females only), increased abdominal swelling, elevated alkaline phosphatase, alanine and aspartate aminotransferases, increased liver weights as well as increased incidence of hepatocellular hypertrophy and chronic inflammation of the lungs. The **CARC** concluded that the liver and lung tumors in male and female mice were treatment-related.

2. Mutagenicity: The CARC determined that the available database was inadequate to fulfill the guideline requirements and identified a data gap for an *in vitro* cytogenetic assay. Four acceptable genetic toxicology studies were available for review. Overall, the data indicate that MON 13900 induced a weak positive response at high precipitating doses in *Salmonella typhimurium* but was negative in cultured mammalian cells. MON 13900 was also negative in the mouse micronucleus assay and did not cause unscheduled DNA synthesis (UDS) in primary rat hepatocytes. Because the available studies do not satisfy the new Subdivision F Guideline requirements for mutagenicity testing and do not exclude the possibility of direct mutagenicity, the CARC recommended that an *in vitro* cytogenetic assay be performed to examine the clastogenic potential of MON 13900. This recommendation was strengthened by the evidence that structurally related chloroacetanilides such as alachlor and acetochlor demonstrated clastogenicity *in vitro*.

3. Structure Activity Relationship: The structurally-related chloroacetanilide compounds, alachlor and acetochlor, are both clastogenic. They share the reactive chloroacetyl sidechain which could contribute to stomach cancer as the common target. However, the quinoneimine activation pathway of alachlor (and probably also of acetochlor) is not applicable to MON 13900. With the exception of stomach cancer, the target spectrum of MON 13900 differs from that of alachlor and acetolachlor. These compounds were classified by the CARC as "likely to be carcinogenic to humans".

4. Mode of Action: No mechanistic studies were submitted by the registrant.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July, 1999), the Committee classified MON 13900 as **"likely to be carcinogenic to humans"** by the oral route based on the following weight-of-the-evidence considerations:

1. Multiple tumors were seen at multiple sites in two species including both benign and malignant liver tumors in male and female rats and mice, rare tumors such as stomach and testicular tumors in male rats and lung tumors in both sexes of mice.

2. The relevance of the observed tumors to human exposure cannot be discounted.

3. Structurally-related compounds, alachlor and acetochlor, cause tumors at multiple sites (liver, stomach, or lung) in rats and/or mice and have been classified by the CARC as "likely to be carcinogenic to humans."

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended the following approach for human risk characterization:

- For human risk characterization, the extrapolation of risk using the linear low-dose (Q_1*) approach for most potent and biologically significant tumor type was recommended. This extrapolation was supported by the increases in the incidence of liver, stomach and testicular tumors as well as lung tumors in one or both sexes of rats or mice, the potential for clastogenic effect, lack of adequate genotoxicity/mutagenicity data, as well as lack of mode of action data.

VIII. BIBLIOGRAPHY

MRID No.	CITATION
42019728	Reyna, M. and Ribelin, W. (1991) Three Month Feeding Study of MON 13900 in Sprague-Dawley Rats. Environmental Health Laboratory, St. Louis, MO. April 30, 1991. EHL 90025. Unpublished. HED Document Nos. 009825, 013247
42019729	Trutter, J. (1991) Subchronic Toxicity Study in Dogs with MON 13900. Hazleton Washington, Inc., Vienna, VA. HL-90-97, HWA 241-226. Unpublished. HED Document Nos. 009825, 013247
42019732	A.M. Kirk (1989). Ames/Salmonella Mutagenicity Assay of MON 13900 Environmental Health Laboratories, Monsanto Company, St Louis, MO; Study No. EHL 88108; dated February 8, 1989. Unpublished. HED Document Nos. 009825, 013379
42019733	Li, A.P. and Myers, C.A. (1989). CHO/HGPRT Gene Mutation Assay with MON 13900; Environmental Health Laboratories, Monsanto Agricultural Company, St. Louis, MO; Study No. ML-88-177; EHL 88075; Date Issued: January 24, 1989. Unpublished. HED Document Nos. 009825, 013379
42019734	J.P. Bakke (1989). Evaluation of the Potential of MON 13900 to Induce Unscheduled DNA Synthesis in the In Vitro Hepatocyte DNA Repair Assay in the Male F-344 Rat; SRI International, Menlo Park, CA; Study No. SRI No. LSC-6889; Monsanto Report No. SR-88-421; dated March 29, 1989. Unpublished. HED Document Nos. 009825, 013379
42980202	Stegman, S.D., Garrett, S.L. and Kier, L.D. (1993) Mouse Micronucleus Study of MON 13900, performed at Monsanto's Environmental Health Laboratory (EHL), St. Louis, MO, Project No. ML-93-62 (EHL Study Number EHL 93009), dated April 26, 1993. Unpublished. HED Document No. 013247.
43700801	Lemen, JK, Ruecker, FA. 1995. Combined Chronic Toxicity/Oncogenicity Study of MON 13900 Administered in Feed to Sprague-Dawley Rats for 24 Months. Monsanto Company (EHL), St. Louis, Missouri. Report No. EHL 91099; Study No. 91265. June 20, 1995. Unpublished. HED Document No. 013247.

43700802 Lemen, JK. 1995. Oncogenicity Study of MON 13900 Administered in Feed to CD-1® Mice for 18 Months. Monsanto EHL, St. Louis, Missouri. Monsanto Study No. ML-92-038; Project No. EHL 01101. June 22, 1995. Unpublished. HED Document No. 013247.

44842701 Danhaus, R. 1999. Historical Control Data -- Additional Information Requested by the Agency Reviewer of the Following Previously Submitted Study: Combined Chronic Toxicity/Oncogenicity Study of MON 13900 Administered in Feed to Sprague-Dawley Rats for 24 Months. MRID No. 43700801. Data Requirement submitted June 3, 1999 by Monsanto Life Sciences Company. Unpublished.

44857801 Danhaus, R. 1999. Historical Control Data -- Additional Information Requested by the Agency Reviewer of the Following Previously Submitted Study: Oncogenicity Study of MON 13900 Administered in Feed to CD-1 Mice for 18 Months. Study/Project Number ML-92-038/EHL 9110. MRID No. 43700802. Data Requirement submitted June 21, 1999 by Monsanto Company. Unpublished.

---------- Brunsman, LL. (1999). "MON 13900 (Furilazole™) Qualitative Risk Assessment Based on Sprague-Dawley Rat and CD-1 Mouse Dietary Studies. May 6, 1999. HED Document No. 013356